CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

1-NAPHTHALENEACETIC ACID
Chemical Code # 423, Tolerance # 155, SB 950 # 164
1-NAPHTHALENEACETIC ACID SODIUM SALT
Chemical Code #761, Tolerance # 50784, SB 950 # 761
1-NAPHTHALENEACETIC ACID, ETHYL ESTER
Chemical Code # 749, Tolerance # 155, SB 950 # 759
1-NAPHTHALENEACETAMIDE
Chemical Code # 422, Tolerance # 309, SB 950 # 765

November 3, 1999
Revised March 9, 2001

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, possible adverse effect [a]
Oncogenicity, rat:	No data gap, possible adverse effect
Oncogenicity, mouse:	Data gap, inadequate study
Reproduction, rat:	No data gap, possible adverse effect
Teratology, rat:	Data gap, inadequate study, possible adverse effect indicated
Teratology, rabbit:	Data gap, inadequate study, possible adverse effect indicated
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	Data gap, inadequate study
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

All record numbers through 50784-010, 150752; 309-016, 145805; and 155-045, 139929 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
File name: T010309
Prepared by Stanton Morris, 11/30/99; revised by J. Gee, 3/9/01
[a] Possible adverse effect was seen in a 6-month study.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

50784-010; 150752; ATwo-year Chronic Toxicity/Oncogenicity Study in Rats with 1-Naphthaleneacetic Acid Sodium Salt (1-Na-NAA) (MRD-92-349),@ Laboratory Project ID 134970B; J. G. Drummond; Exxon Biomedical Laboratory, East Millstone, NJ; 10/16/96. Groups of 80 Crl:CD BR rats/sex were fed dietary mixtures of 1-Naphthalene Acetic Acid Sodium Salt (1-Na-NAA, lot No. 214001, 96.44% stated purity) at 0, 100, 1000, or 5000 ppm. Twenty animals/sex/dose were sacrificed at 12 months with the remainder being sacrificed between 20.5 and 23 months (moribund animals sacrificed early). Cageside observations were made 5 days/week. Clinical observations, body weight, and food consumption were measured weekly. Hematology, serum chemistry, and urinalysis were performed on 10 rats/sex/group after 6, 12 and 18 months of dosing and at termination. Ophthalmoscopic examinations were done pretest, 12 months, and at termination. All animals that were sacrificed at 12 months and at termination were necropsied and organs weighed. The NOEL for chronic toxicity was 100 ppm based on treatment-related effects seen in females at 1000 and 5000 ppm that included: decreased body weight gain (terminal body weights were respectively 90 and 66% of controls), decreased food consumption, and Increased focal alveolar macrophages Other treatment-related effects seen at 5000 ppm included increased serum alkaline phosphatase in both sexes at all time points; decreased serum triglyceride levels in both sexes at 6, 12, and 18 months and at 24 months lowered in females and raised in males; decreased urine protein in females; increased glandular stomach dilated mucosal glands in both sexes; and focal chronic alveolar inflammation in females. A **possible adverse oncogenic effect** was indicated by an increased incidence in benign endometrial stromal polyps in females at 5000 ppm. The high dose did not adequately characterize chronic toxicity in males. The study was unacceptable but upgradeable with submissions that identifying the target organ(s) in males for chronic exposure (S. Morris and J. Gee, 12/5/97).

155-047 179559 This submission consisted of a report amendment for record 150752 above containing notations of revisions and a revised protocol as Supplement 1, dated November 10, 2000. Accompanying the volume was a letter, dated November 10, 2000, from ExxonMobil Biomedical Sciences, Inc., addressing two items in the worksheets for record 150752 regarding randomization of animals and dose selection. Since the data gaps for oncogenicity and chronic studies in the rat had been filled, there was no change in status due to these submissions. (Gee, 3/8/01)

Note: The possible adverse effect was listed under the rat oncogenicity test type.

50784-003; 126288; A90-Day Dietary Toxicity Study in Rats with 1-Naphthaleneacetic Acid - Sodium Salt (1-Na-NAA),@ Laboratory Project ID 134970A; R.T. Plutnick; Exxon Biomedical Sciences, Inc., East Millstone NJ; 9/8/93. Groups of 10 Crl:CDBR Sprague-Dawley rats/sex were fed 1-naphthaleneacetic acid sodium salt (1-Na-NAA, lot no. 214001, 96.44% stated purity) in the diet at 0, 200, 2000, or 8000 ppm for 90 days. Clinical observations were made daily; body weights and food consumption were determined weekly; hematology and serum chemistry were done at termination; a urinalysis was done prior to termination; ophthalmoscopic examinations were done pre-treatment and in the final week; gross pathology examinations were done on all animals; and histopathology examinations were done on control and high dose animals, animals sacrificed before study termination, and gross lesions from low and mid-dose groups. Treatment-related effects were: decreased body weight gain and food consumption in both sexes at 8000 ppm with group mean body weights approximately 80% of controls; decreased hemoglobin and hematocrit in both

sexes at 8000 ppm and females at 2000 ppm; decreased total protein and albumin in males at 8000 ppm; urine glucose increased in males and decreased in females at 8000 ppm; increased relative liver and kidney weights in both sexes at 8000 ppm; hepatocellular hypertrophy in both sexes at 8000 ppm (M: 4/10, F: 4/10 vs. 0/10 for controls); increased vacuolation of periportal hepatocytes in females at 2000 (10/10) and 8000 ppm (10/10 vs. 2/10 for controls); hypertrophy of adrenal gland zona glomerulosa in both sexes at 8000 ppm (M: 3/10, F: 7/10) and females at 2000 ppm (6/10 vs. controls M: 0/10, F: 2/10); and hypertrophy of urinary bladder superficial mucosal cells in both sexes at 8000 ppm (M: 9/10, F: 7/10 vs. controls M: 2/10, F: 2/10) (NOEL = 200 ppm). Mean test material intake for week 13 at 8000 ppm was 404 mg/kg/day (M) and 484 mg/kg/day (F). No adverse effect was indicated. No worksheet was done. The study was acceptable (J. Gee and S. Morris, 12/5/97).

Summary: The combined study was adequate to fill the data gap for the rat oncogenicity test type. The rat chronic toxicity data gap is filled by the collective data in the 90-day and two-year studies which adequately characterize the chronic toxicity of the test material.

CHRONIC TOXICITY, RAT

See Combined, Rat above.

CHRONIC TOXICITY, DOG

50784-007; 138882; AA 52-Week Oral (Capsule) Toxicity Study of 1-Naphthaleneacetic Acid Sodium Salt in the Beagle Dog,@ Laboratory Project ID 85212; Lynn Kansas; Bio-Research Laboratories Ltd., Senneville, Quebec; 5/16/95. Groups of 4 beagle dogs/sex received oral doses (in gelatine capsules) of 1-naphthaleneacetic acid sodium salt (batch lot # 214001, 96.44% purity) at 0, 15, 75, or 250 mg/kg/day for 52 weeks. There were no treatment-related changes in survival, clinical signs, body weight gains, food intake, ophthalmology, hematology, clinical chemistry, urinalysis, organ weight measurements, or gross pathology. Treatment-related effects were: an increased incidence of emesis and slight sinusoidal histiocytosis of the liver in both sexes at 225 mg/kg/day and, in males, increased incidences of stomach lesions at 75 (3/4) and 225 (3/4) mg/kg/day (severity not dose-related, N0EL = 15 mg/kg/day). **No adverse effect was indicated. The study was acceptable (S. Morris and J. Gee, 1/28/98).

50784-004; 126739; AA 13-week Oral (Capsule) Toxicity Study of 1-Naphthaleneacetic Acid Sodium Salt in the Beagle Dog,@ Laboratory Project I.D. 85211; L. Kansas; Bio-research Laboratories Ltd., Senneville, Quebec, Canada; 10/14/99. Groups of 4 beagle dogs/sex received oral doses (in gelatine capsules) of 1-naphthaleneacetic acid sodium salt (batch lot # 214001, 96.44% purity) at 0, 25, 150, or 450 mg/kg/day for 13 weeks. Treatment-related effects seen in both sexes at 450 mg/kg/day included: increased emesis and salivation; decreased food intake and body weight gain (13-week body weights were 73% (M) and 75% (F) of controls); lowered red blood cell count, hematocrit, and hemoglobin levels; increased serum levels of aspartate aminotransferase, alanine aminotransferase, and total bilirubin; and increased relative liver weights. Gastrointestinal lesions and bone marrow hypocellularity were seen in both sexes at 150 and 450 mg/kg/day. Small prostate (4/4), testes (3/4), and epididymae (3/4), atrophied testes (4/4), and hypo/aspermia (4/4) were seen in males at 450 mg/kg/day (NOEL = 25 mg/kg/day, MTD = 450 mg/kg/day). The study was acceptable. No worksheet was done (S. Morris and J. Gee, 1/28/98)

155-034; 116326; ASix Month Oral Toxicity Study of Naphthalene Acetic Acid in Beagle Dogs,@ Project No. 1395; DE Morita, DI Hepler, LS Beck & WH Halliwell; ELARS Bioresearch Laboratories,

Fort Collins, CO; 8/1/79. Groups of 4 beagles / sex were given oral doses of naphthalene acetic acid (lot # 16388, gelatin capsules, purity not stated) at 0, 50, 150, or 300 mg/kg/day for 6 months. Daily clinical observations, twice-weekly food consumption, and weekly body weights were recorded. Physical and ophthalmological examinations and urinalyses were done at predose, 3 months, and 6 months. Clinical chemistry determinations were done predose and once a month thereafter. At termination, all animals were subjected to complete gross and histopathological examinations of tissues and organs. Treatment-related signs seen in both sexes at 300 mg/kg/day included transient anorexia, tender mouths, icteric and pale mucous membranes, lethargy, uncoordinated gait, dark urine and stools, and moderate alterations in hematology and clinical chemistry. Female body weight gains were significantly decreased at 300 mg/kg/day. At 300 mg/kg/day, relative kidney weights were increased in both sexes and female absolute liver weights were decreased and adrenal, heart, and brain relative weights were increased. A **possible adverse effect** was indicated by retinal edema and uveitis in 2/4 females at 300 mg/kg/day and treatment-related microscopic liver changes at 50, 150, and 300 mg/kg/day (NOEL < 50 mg/kg/day). The study is unacceptable and not upgradeable because exposures were for 6 months, a NOEL was not determined, there were no analytical data, and page 17 was missing (S. Morris and J. Gee, 3/9/99).

ONCOGENICITY, RAT

See Combined, Rat above

ONCOGENICITY, MOUSE

155-035; 116327; AEvaluation of Carcinogenic, Teratogenic, and Mutagenic Activities of Selected Pesticides and Industrial Chemicals,@ Bionetics Research Labs., Inc.; 8/68. Two groups of eighteen B6C3F1 or B6AKF1 mice/sex were exposed to1-Naphthalene acetamide (J.T. Baker, m. p. 183-184EC). One group received a single subcutaneous injection of 46.4 mg/kg (DMSO solvent) in the nape of the neck at approximately 28 days of age. The second group was given 464 mg/kg/day (0.5% gelatin vehicle), daily by oral gavage on 7 through 28 days of age followed by dietary mixtures of 1298 mg/kg until termination. All mice were terminated at 18 months of age and examined for tumors. Neither route of exposure appeared to produce elevated levels of tumors when compared to controls. Many other compounds were also screened for tumor formation. The study contained minimal experimental details and only summary tables of data that were not adequate for detailed evaluation. The study is unacceptable. No worksheet was done (S. Morris and J. Gee, 3/16/99).

REPRODUCTION, RAT

****50784-008; 141498;** ATwo Generation Reproduction Toxicity Study in Rats with 1-Naphthaleneacetic acid sodium salt (1-Na-NAA) (MRD-92-349),@ Laboratory Project ID 134935; G.W. Trimmer; Exxon Biomedical Laboratory, East Millstone, NJ; 8/18/95. Groups of 35 Crl:CDBR rats/sex (P1) were fed diets containing 1-Naphthaleneacetic acid sodium salt [lot # P/O 22726 (214001), 96.44%] at 0, 100, 1000, or 3000 ppm continuously for 10 weeks prior to mating and through one mating period. Exposures continued for the P1 females through gestation and postpartum until weaning of the F1 offspring on postpartum day 21 (PPD 21). Selected F1 offspring (P2) were exposed from PPD 21 for at least 10 weeks and through one mating period. Exposures continued for the P2 females through gestation and postpartum until weaning of the F2 offspring on PPD 21. P1 and P2 males were sacrificed after birth of their sired pups. P1 and P2 females were sacrificed following weaning of their pups on PPD 21. F1 and F2 litters were culled to approximately 4 pups/sex/litter on post natal day 4 (PND 4), weaned and sacrificed on PND 21, and 10 pups/sex/group were sacrificed and examined internally. Gross necropsies and

microscopic examinations were done on all P1 and P2 adults and 10 F1 and F2 pups/sex/group. A treatment-related decrease in body weight gain was seen in P1 and P2 females and P2 males at 3000 ppm (adult NOEL = 1000 ppm). A **possible adverse reproductive/developmental effect** was indicated by decreased birth weight, decreased body weight gain, and decreased survival seen at 3000 ppm in both sexes of the F1 and F2 pups (developmental NOEL = 1000 ppm). A rangefinding study was an adequate rationale for the high dose (see 50784-006, 128691). The study was acceptable (S. Morris and J. Gee, 11/29/99).

50784-008; 141498: A multigeneration range finding study was summarized in which groups of unspecified numbers of rats were exposed for 3 weeks to 200, 1000, or 6000 ppm 1-naphthaleneacetic acid sodium salt. At the end of the 3 weeks, the 6000 ppm group mean body weights were 90% of controls. Gestation body weight and food consumption at 6000 ppm. A **possible adverse effect** was indicated by the decreased offspring survival and body weight at 6000 ppm. The mean body weight of the 1000 ppm female pups was 87 to 94% of controls. No effects were reported at 200 ppm. No other information about this study was presented. No worksheet was done (S. Morris, 3/2/99).

50784-008; 141498: A 90-day toxicity study was summarized in which the 8000 ppm (both sexes) and 2000 ppm (females) group mean body weights were, respectively, 81% and 96% of controls and food consumptions were down. No effects were reported at 200 ppm. No other information about this study was presented. No worksheet was done (S. Morris, 3/2/99).

50784-008; 141498: A chronic toxicity study was summarized in which the 5000 ppm group mean body weights for males and females were respectively 91 and 86% of controls. Food consumption was down in females. Similar effects were seen in the 5000 ppm females as were seen in the 6000 ppm females in the multigeneration range finding study above. No other information about this study was presented. No worksheet was done (S. Morris, 3/2/99).

Letter dated November 15, 1993; no DPR doc. #. This 2-page document contains preliminary results of a 2-generation rat reproduction study (GL 83-4). Groups of 10 rats/sex were fed dietary mixtures of 0, 200, 100, or 6000 ppm 1-naphthleneacetic acid sodium salt. Adverse clinical signs, decreased body weight gain, and decreased food consumption were in adults at seen at 6000 ppm. A **possible adverse effect** was indicated by decreased live litters, live litter size, and fetal and pup survival at 6000 ppm. No worksheet was done (S. Morris, 1/20/98).

50784-006; 128691; AMultigeneration Reproduction Toxicity Rangefinding Study in Rats with 1-Na-NAA (MRD-92-349),@ Lab. Project ID 134933; R. D. Phillips; Exxon Biomedical Sciences, Inc., East Millstone, NJ; 2/17/94. Groups of 10 rats/sex fed diets containing 1-naphthalene acetic acid sodium salt (lot # P/O 22726 (214001), 96.44% 1-NAA, 1.79% 2-NAA) at 0, 200, 1000, or 6000 ppm (average measured doses, mg/kg/day - male: 12.3, 61.9, 361; female: 13.4, 65.5, 356) continuously for 3 weeks prior to mating and through one mating period. Exposures were continued for the P1 females through gestation and postpartum until weaning of the F1 offspring on postpartum day 21 (PPD 21). All F1 offspring were exposed from PPD 21 to 28. P1 males were sacrificed at the end of the mating period. P1 females were sacrificed following weaning of their pups on PPD 21. F1 pups were sacrificed on postnatal day 28. Gross necropsies and microscopic examinations were done on all P1 adults and F1 pups who died during the study. Adult uteri were examined grossly for evidence of implantation. One 6000-ppm female apparently died from dystocia on gestation day 21 (GD 21). Treatment-related decreases in body weight was seen at 6000 ppm with male body weights being 91.8% and 89.6% of controls on the respective treatment days 21 and 42. Female body weights were 89.5% of

controls on treatment days 21 and 87% and 77% of controls on the respective gestation days 0 and 21. Treatment -related decreases in food consumption were seen in both sexes at 6000 ppm. A **possible adverse effect** was indicated at 6000 ppm by treatment-related decreases in group mean live litter size, % live pups, pup weight, and pup survival and increased still births (developmental NOEL = 1000 ppm). The study was acceptable supplemental data that adequately justified the doses used in the main study. No worksheet was done (S. Morris, 11/29/99).

TERATOLOGY, RAT

155-036; 116328; ATeratology Study with NAA Acid (Technical) by Gavage in the Albino Rat@ HRC #R-4216-4 (1-350); K. McElroy, T.J. Miller, and C. O. Ward; Huntingdon Research Center, New City, NY; 1/14/77. Groups of 24 pregnant albino CD rats were given 1-Naphthalene Acetic Acid (technical, lot #NAA 73323G, unstated purity, suspended in carboxymethyl cellulose, 10 ml/kg) by gastric intubation on gestation days 6 through 15 at 0, 10, 50, or 250 mg/kg/day. Dams were sacrificed on gestation day 20 and their ovaries, uteri, and fetuses were examined. Maternal effects included reduced body weight gain at 250 mg/kg/day (maternal NOEL = 50 mg/kg/day) that may be due to decreased uterine weight gain. Treatment-related fetal abnormalities and malformations were not seen. A **possible adverse effect** was indicated by decreased mean implantations and litter sizes at 50 and 250 mg/kg/day (developmental NOEL = 10/mg/kg/day). The study is unacceptable but possibly upgradeable with submission of mean body weights corrected for uterine weights for all animals, complete uterine and ovarian data for all animals, complete individual adult body weight data, historical control data for abortions, total litter deaths, total litter resorptions, fetal viability, implantations, resorptions, corpora lutea, pre and post implantation loss, detailed descriptions of resorption determinations and implantation and preimplantation calculations, and statistical tests and analysis of the test material (S. Morris and J. Gee, 11/24/98).

155-036; 116328; ATen-Day Range Finding Study with NAA by Daily Gavage to Rats,@ HRC #R-4216-4; K.E. McElroy and C.O. Ward; Huntingdon Research Center, New City, NY; 8/16/76) in which groups of 3 Sprague-Dawley rats per sex were dosed by daily oral gavage with NAA 733236 for 10 days at 0, 250, 1000, or 4000 mg/kg/day. Treatment-related effects were seen in both sexes: ataxia and lethargy at 1000 and 4000 mg/kg/day, prostration at 4000 mg/kg/day, decreased weight gain at 1000 mg/kg/day, and lethality - 1/6 (female) at 1000 mg/kg/day and 6/6 (both sexes) at 4000 mg/kg/day. No worksheet was done (S. Morris and J. Gee, 11/24/98).

155-022; 037296: Duplicate of doc. # 155-036 rec. # 116328.

TERATOLOGY, RABBIT

155-036; 116334; ATeratology Study in Rabbits,@ 369-105; L.G. Miller, J.L. Schardein, and M. Blair; International Research and Development Corporation, Mattawan, MI; 11/28/83. Groups of 16 artificially inseminated Dutch Belted rabbits (chorionic gonadotropin, iv,100 USP units/rabbit) were given single daily doses by oral gavage of naphthalene acetic acid (lot # RTS2846AC, 98.55% stated purity; 0.5% methylcellulose vehicle, 3.0 ml/kg) on gestation days 7 through 27 at 0, 37.7, 75, or 150 mg/kg/day. Dams were sacrificed on gestation day 28. The uteri, ovaries, fetuses, and the abdominal and thoracic cavities and organs were examined. All fetuses were examined for external and internal malformations and variations and then stained and examined for skeletal malformations and variations. There was one maternal lethality at 37.5 mg/kg/day and three at 150 mg/kg/day. There were no treatment-related maternal effects (maternal NOEL>= 240 mg/kg/day based on pilot study). A **possible adverse effect** was indicated by a treatment-related decrease in mean implantations and fetal viability at 150 mg/kg/day in the main study and at 80 and 240

mg/kg/day in a pilot study (reproductive NOEL = 37.7 mg/kg/day). The study is not acceptable but possibly upgradeable with submission of adequate analytical data for the dosing material (S. Morris and J. Gee, 12/28/98).

155-036; 116330; ARange-Finding Teratology Study in Rabbits,@ 369-111; B. H. Cuddeback, J. L. Schardein, and M. Blair; International Research and Development Corporation, Mattawan, MI; 10/28/83. Groups of 5 presumed-pregnant Dutch Belted rabbits were given single daily doses by oral gavage of naphthalene acetic acid (lot # RTS2846AC, 98.55% stated purity; 0.5% methylcellulose vehicle, 3.0 ml/kg) on gestation days 6 through 27 at 0, 28, 80, or 240 mg/kg/day. One 80 mg/kg/day rabbit died and one 240 mg/kg/day rabbit aborted. There were no treatment-related maternal effects. There were treatment-related decreases in mean implantations and viable fetuses at 80 and 240 mg/kg/day. No worksheet was done (S. Morris and J. Gee, 12/28/98).

155-022; 037207: Duplicate of doc. # 155-036, rec. # 116330.

155-022; 037207: Duplicate of doc. # 155-036, rec. # 116334.

GENE MUTATION

**155-045; 139928; A*Salmonella* Plate Incorporation Mutagenicity Assay (Ames Test) with a Confirmatory Assay,@ Laboratory Study Number G94AU53.501001; R. H. C. San and M. L. Klug; Microbiological Associates, Inc., Rockville, MD; 12/02/94. The rate of reverse mutation rates of histidine auxotrophic *Salmonella* tester strains (TA98, TA100, TA1535, TA1537, TA1538) to heterotrophy was measured in the presence and absence of metabolic activation (S9 supernatants of Aroclor 1254-induced, male, Sprague-Dawley rat liver homogenates) and 1-naphthaleneacetic acid, ethyl ester (NAAEE, lot # AM315002, 97.75%, DMSO vehicle). Mixtures of selective agar with or without S9, varying concentrations of NAAEE, and • 3 X 10^7 cells / plate were incubated for 48 to 72 hours and the resulting colonies were counted. A range finding trial was conducted with TA100 cells and 0, 6.7, 10, 33, 67, 100, 333, 667, 1000, 3333, or 5000 ug NAAEE / plate. Two trials were conducted in triplicate with TA98, TA100, TA1535, TA1537, and TA1538 cells at 0, 33, 100, 333, 667, 1000, or 5000 ug NAAEE / plate. Positive controls were adequate. There was no treatment-related increase in colony formation. No adverse effect is indicated. The study is acceptable (S. Morris and J. Gee, 3/4/99).

**155-045; 139929; A*Salmonella* Plate Incorporation Mutagenicity Assay (Ames Test) with a Confirmatory Assay,@ Laboratory Study Number G94AU54.501001; R.H.C. San and M. L. Klug; Microbiological Associates, Inc., Rockville, MD; 2/6/95. The rate of reverse mutation rates of histidine auxotrophic *Salmonella* tester strains (TA98, TA100, TA1535, TA1537, TA1538) to heterotrophy was measured in the presence and absence of metabolic activation (S9 supernatants of Aroclor 1254-induced, male, Sprague-Dawley rat liver homogenates) and 1-naphthaleneacetamide (lot # I 940415, 98.7%, DMSO vehicle). Mixtures of selective agar with or without S9, varying concentrations of naphthaleneacetamide, and • 3 X 10^7 cells / plate were incubated for 48 to 72 hours and the resulting colonies were counted. A range finding trial was conducted with TA100 cells and 0, 6.7, 10, 33, 67, 100, 333, 667, 1000, 3333, or 5000 ug / plate. Two trials were conducted in triplicate with TA98, TA100, TA1535, TA1537, and TA1538 cells at 0, 33, 100, 333, 667, 1000, or 5000 ug / plate. Positive controls were adequate. There was no treatment-related increase in colony formation. No adverse effect is indicated. The study is acceptable (S. Morris and J. Gee, 3/8/99).

155-037; 116335; @Ames Salmonella/Microsome Plate Test (with and without metabolic activation) on: Amchem 1-Nahphthalene Acetic Acid@; R. J. Matthews and R. W. Naismith; Pharmakon Laboratories, Scranton PA; 5/11/78. Mutation rates were measured for reversion of histidine

auxotrophic strains of Salmonella typhimurium (TA1535, TA1537, TA1538, TA98, TA100) to prototrophy. Bacteria were mixed with growth medium containing 1-naphthalene acetic acid (lot GN-2095) at 0, 0.5, 2, 8, 40, 200, 1000, or 5000 ug/plate with or without metabolic activation (S9 supernatants of centrifugates of Aroclor-induced, male Sprague-Dawley rat liver homogenates). One plate/strain/dose was incubated for 2 days and the resulting reverent colonies counted. There were no treatment-related effects on reverent colony formation. **No adverse effect** was indicated. The study was unacceptable and not upgradeable because there was no statement of purity and no analytical data for the test material or dosing materials, there was one trial with two plates/strain/dose, exposure concentrations were not stated for the positive controls, and there were no individual plate counts. (S. Morris and J. Gee, 3/24/99).

155-021; 037199: Duplicate of doc. # 155-037, rec. # 116335.

155-037; 116339; Yeast (Saccharomyces cerevisiae) Strain D-7 Reverse Mutation Assay on: 1-Nahphthalene Acetic Acid, Lot GN-2095@; R. J. Matthews and R. W. Naismith; Pharmakon Laboratories, Scranton PA; 6/17/78. Mutation rates were measured for reversion of an isoleucine auxotrophic strain of Saccharomyces cerevisiae (D-7) to prototrophy. Samples of washed yeast cells were incubated in solutions of 1-naphthalene acetic acid (lot GN-2095) at 0, 10^{-2}, 10^{-3}, 10^{-4}, 10^{-5}, or 10^{-6} M for one hour, centrifuged, washed, and then 20 replicates per dose were plated on isoleucine-free medium, incubated for 6 to 10 days, and scored for reverent colonies. There was no treatment-related effect on the frequency of reverent colony formation. **No adverse effect** was indicated. The study was unacceptable and not upgradeable because there was no trial with metabolic activation, no statement of purity for the test material, no analytical data for the test material or dosing materials, one trial, inadequate rationale for the treatment levels, incomplete protocol, no raw viability data, and no GLP or QA statements (S. Morris and J. Gee, 3/29/99).

155-021; 037201: Duplicate of doc. # 155-037, rec. # 116339.

155-037; 116348: ASurvey on Mutagenicity of Pesticides by the Salmonella-Microsome Test;@ N. Nishimura, H. Nishimura, and H. Oshimo; J. Aichi Med. Univ. Assoc., Vol. 10, No. 4, pp 305-312, 10/15/82. This document contained no data on 1-naphthalene acetic acid. The document reported that 2-naphthalene acetic acid at 0.8 umole/plate, with and without metabolic activation, did not increase reversion frequency of TA100 and TA98 tester strains. The report stated that a-NAA (1-NAA) was used but the data table indicates ß-NAA (2-NAA) was used. The study was unacceptable. No worksheet was done (S. Morris, 4/15/99).

155-037; 116349; AFurther Mutagenicity Studies on Pesticides in Bacterial Reversion Assay Systems;@ M. Moriya, T. Ohata, K. Watanabe, T. Miyazawa, K. Kato, and Y. Shirasu; Mutation Research, Vol. 116, pp. 185-216, 1983. The document reported that 1-naphthalene acetic acid at an unspecified concentration, with and without metabolic activation, did not increase reversion frequency of TA100, TA98, T1535, TA1537, and TA1538 strains of Salmonella typhimurium or WP2 hcr strain of Escherichia coli. No other information was given. No worksheet was done (S. Morris, 4/15/99).

CHROMOSOME EFFECTS

**155-044; 139926; AMicronucleus Cytogenetic Assay in Mice,@ Lab. Study No. G94AU54.122; D. L. Putman and R. R. Young; Microbiological Associates, Inc., Bethesda, MD; 11/30/94. Groups of 20 ICR mice/sex were given single ip injections (20 ml/kg) of 1-naphthaleneacetamide (lot # 940415, 98.7% stated purity, 1% carboxymethyl cellulose vehicle) at 0, 250, 500, or 1000 mg/kg. Mortality at 1000 mg/kg was 1/20 males and 4/20 females. Clinical signs were lethargy in all mice at 500 and 1000 mg/kg and piloerection in one female at 1000 mg/kg. Groups of 5 mice/sex were sacrificed at 24, 48, or 72 hours after exposure and 1000 polychromatic erythrocytes (PCE) in

bone marrow smears were microscopically examined for the number of micronucleated PCE per 1000 PCE and PCE per 1000 erythrocytes. Treatment-related decreases were seen in the PCE:erythrocyte ratio but not the micronucleated PCE:PCE ratio. The positive control was adequate. **No adverse effect** was indicated. The study was acceptable (S. Morris and J. Gee, 1/27/99).

155-037; 116347; @Dominant Lethal Study (1-Napthalene Acetic Acid - 16388),@ Study No. PH-307-AM-118 NAA; R. W. Naismith and R. E. Panasevich; Pharmakon Laboratories, Scranton PA; 2/28/79. Groups of 10 male Sprague-Dawley rats were given 1-naphthalene acetic acid (lot 16388, purity not stated, suspended in 0.25% methylcellulose, 20 ml/kg) by oral gavage at 0, 125, 250 or 500 mg/kg/day for 5 days. Twenty-four hours after the fifth dose, each male was co-housed with 2 virgin females / week for 8 weeks. The females were sacrificed 14 days from mid-week of mating and the number of corpora lutea and live and dead implants were recorded. There was no treament-related effect on implantation loss. **No adverse effect** was indicated. The study is unacceptable and but possibly upgradeable with adequate submission of a justification for using 10 males/dose, rationale for dose selection, individual male body weight data, a statement of purity, and analytical data for the test or dosing materials (S. Morris and J. Gee, 4/14/99).

155-021; 037205: Duplicate of doc. # 155-03, rec.# 116347.

155-044; 139927; AMicronucleus Cytogenetic Assay in Mice,@ Lab. Study No. G94AU53.122; D. L. Putman and R. R. Young; Microbiological Associates, Inc., Bethesda, MD; 12/12/94. Groups of 20 ICR mice/sex were given single ip injections (20 ml/kg) of 1-naphthaleneacetic acid, ethyl ester (lot # AM 315002, 97.75% stated purity, 1% carboxymethyl cellulose vehicle) at 0, 305, 610, or 1220 mg/kg. Mortality at 1220 mg/kg was 11/20 males and 8/20 females. Clinical signs were lethargy in both sexes at 610 and 1220. Groups of 5 mice/sex were sacrificed at 24, 48, or 72 hours after exposure and 1000 polychromatic erythrocytes (PCE) in bone marrow smears were microscopically examined for the number of micronucleated PCE per 1000 PCE and PCE per 1000 erythrocytes. Treatment-related decreases were seen in the PCE:erythrocyte ratio but not the micronucleated PCE:PCE ratio. The positive control was adequate. **No adverse effect was indicated. The study was acceptable (S. Morris and J. Gee, 1/27/99).

155-037; 116346; @Perform the Micronucleus Test According to S.O.P. PH 309 on: 1-Naphthalene Acetic Acid (NAA), Lot GN-2095,@ Study No. PH-309-AM19-NAA; R. J. Matthews and R. W. Naismith; Pharmakon Laboratories, Scranton PA; 1/30/79. Groups of 4 CF-1 mice / sex were given daily i.p. doses of 1-naphthalene acetic acid (lot GN-2095) at 0, 60, or 125 mg/kg/day for two days. Six hours after the second dose, the animals were sacrificed and femural bone marrow samples were taken and prepared for microscopic examination of 1000 polychromatic erythrocytes / mouse for the presence of micronuclei. There were no treatment-related signs of toxicity or effects on micronuclei. **No adverse effect** was indicated. The study is unacceptable and not upgradeable because there was no statement of purity for the test material, no analytical data for the test material or dosing materials, an inadequate number of mice / dose, inadequate rationales for the treatment schedule and doses, and no GLP or QA statements (S. Morris and J. Gee, 3/30/99).

155-021; 037203: Duplicate of doc. # 155-037, rec. # 116346.

DNA DAMAGE

155-037; 116343 @Escherichia coli DNA Polymerase I Deficient Assay on: 1-Naphthalene Acetic acid@; R. J. Matthews and R. W. Naismith; Pharmakon Laboratories, Scranton PA; 7/27/78. The toxicity of 1-naphthalene acetic acid (lot GN-2095, 10% DMSO solvent) was measured in DNA repair deficient (p3478) and competent (W3110) strains of Escherichia coli. Solid media seeded with bacteria was overlayed with 7 mm discs impregnated with 10 ul of 0, 1, 2, or 4 mg/ml solutions

of the test material with or without S-9 metabolic activation system (supernatants of 9000 g centrifugates of Aroclor-induced, male Sprague Dawley rate liver homogenates). There were four replicates for each treatment. After 16 hours, the zone of inhibition of bacterial growth around each disc was measured. **No adverse effect** was indicated. The study was unacceptable and not upgradeable because there was no statement of purity and no analytical data, the concentrations of the positive controls were not stated; there were no GLP or QA statements, and the technique relies on differential toxicity to two strains of bacteria but toxicity was not demonstrated in either strain (S. Morris and J. Gee, 4/21/99).

155-021; 037202: Duplicate of doc. # 155-037, rec. # 116343.

155-037; 116341; @Yeast (Saccharomyces cerevisiae) Strain D-7 Mitotic Gene Conversion Assay on: 1-Nahphthalene Acetic Acid@; R. J. Matthews and R. W. Naismith; Pharmakon Laboratories, Scranton PA; 7/20/78. Mitotic gene conversion rates at the tryptophan locus from a tryptophan-requiring to a non-tryptophan-requiring phenotype were measured in trp 5-12 / trp 5-27 strain D-7 of Saccharomyces cerevisiae. Samples of washed yeast cells were incubated in solutions of 1-naphthalene acetic acid (lot GN-2095) at 0, $2.1X10^{-2}$, 10^{-2}, $5.4X10^{-3}$,10^{-3},10^{-4},10^{-5}, or 10^{-6} M for one hour, centrifuged, washed, and then 30 replicates per dose were plated on tryptophan-free medium, incubated for 6 to 10 days, and scored for convertant colonies. There was no treatment-related effect on the frequency of convertant colony formation. **No adverse effect** was indicated. The study was unacceptable and not upgradeable because there was no trial with metabolic activation, no statement of purity for the test material, no analytical data for the test material or dosing materials, inadequate rationale for the treatment levels, incomplete protocol, no raw viability data, and no GLP or QA statements (S. Morris and J. Gee, 3/30/99).

155-021; 037204: Duplicate of doc. # 155-037, rec. # 116341.

155-021; 037200; @Yeast (Saccharomyces cerevisiae) Strain D-7 Mitotic Crossing Over on: 1-Nahphthalene Acetic Acid, Lot GN-2095@; R. J. Matthews and R. W. Naismith; Pharmakon Laboratories, Scranton PA; 7/19/78. Mitotic cross-over rates were measured for two alleles of the ade2 locus (ade2-40, ade2-119) in heterozygous diploid Saccharomyces cerevisiae (D-7). Samples of washed yeast cells were incubated in solutions of 1-naphthalene acetic acid (lot GN-2095) at 0, 10^{-2}, 10^{-3}, 10^{-4}, 10^{-5}, or 10^{-6} M for one hour, chilled, centrifuged, and washed. Forty replicates per dose were then plated on low adenine medium, incubated for 6 to 8 days, and scored for segregation of the ade2 alleles. Heterozygotes produced white colonies while recombination produced twin sectored red homoallelic ade2-40 / pink homoallelic ade2-119 colonies. There was no treatment-related effect on the frequency of twin sector formation. **No adverse effect** was indicated. The study was unacceptable and not upgradeable because there was no trial with metabolic activation, no statement of purity for the test material, no analytical data for the test material or dosing materials, one trial, inadequate rationale for the treatment levels, no raw data, and no GLP or QA statements (S. Morris and J. Gee, 11/29/99).

155-037; no rec. #: Duplicate of doc. # 155-021, rec. # 037200.

NEUROTOXICITY

Not required at this time.

SUPPLEMENTAL

**50784-005; 128553; A21-day Repeated Dermal Dose Toxicity Study in Rats with 1-Naphthaleneacetic Acid Sodium Salt (1-Na-NAA),@ Laboratory Project ID 134910B; G.W. Trimmer;

Exxon Biomedical Laboratory, East Millstone, NJ; 2/8/94. Groups of 5 Crl:CDBR rats/sex were treated by dermal application of 1-naphthaleneactic acid sodium salt (lot # 214001, 96.44% purity) at 0, 100, 300, or 1000 mg/kg (assuming 100% purity). The test material was applied 6hours/day, 5 days/week for 3 weeks to a clipped dorsal area of skin (approximately 10% of the body surface) and covered with a gauze patch moistened with 1 ml reverse osmosis water per g of test material. Clinical observations, dermal irritation evaluations, and measurements of body weight and food consumption were made at regular intervals. Hematology, serum chemistry, urinalysis, and ophthalmology tests and terminal gross necropsies were performed on treatment day 21. Skin and selected tissues were examined for histopathology. The only treatment-related effect reported were slight microscopic changes in treated skin at 1000 mg/kg: hyperplastic sebaceous glands and epidermal hyperplasia and hyperkeratosis (NOEL = 300 mg/kg). **No adverse effect** was indicated (systemic NOEL $\geq$ 1000 mg/kg). The study was acceptable (S. Morris and J. Gee, 1/23/98).

155-043; 139924;** A21-day Repeated Dermal Toxicity Study in Rats with 1-Naphthaleneacetic Acid, Ethly Estert (MRD-94-835),@ Laboratory Project ID 183510B; G.W. Trimmer; Exxon Biomedical Laboratory, East Millstone, NJ; 3/2/95. Groups of 5 Crl:CDBR rats/sex were treated by dermal application of 1-naphthaleneacetic acid, ethyl ester (lot # AM 315002, 97.75% purity) at 0, 100, 300, or 1000 mg/kg (assuming 100% purity). The test material was applied 6 to 6.5 hours/day, 5 days/week for 3 weeks to a clipped dorsal area of skin (approximately 10% of the body surface) and covered with a gauze patch moistened with 1 ml reverse osmosis water per g of test material and secured with tape. Clinical observations, dermal irritation evaluations, and measurements of body weight and food consumption were made at regular intervals. Hematology and serum chemistry tests and terminal gross necropsies were performed on treatment day 21. Skin and selected tissues were examined for histopathology. The only treatment-related effects reported were mild microscopic changes in treated skin at 100, 300, and 1000 mg/kg: hyperplastic sebaceous glands and epidermal hyperplasia, hyperkeratosis, and dermal inflammatory cell infiltration (NOEL < 100 mg/kg). **No adverse effect** was indicated (systemic NOEL $\geq$ 1000 mg/kg). The study was acceptable (S. Morris and J. Gee, 2/4/99).

155-043; 139925; A21-day Repeated Dermal Toxicity Study in Rats with 1-Naphthaleneacetamide (MRD-94-834),@ Laboratory Project ID 183410B; G. W. Trimmer; Exxon Biomedical Laboratory, East Millstone, NJ; 3/2/95. Groups of 5 Crl:CDBR rats/sex were treated by dermal application of 1-naphthaleneacetamide (lot # I 940415, 98.7% purity) at 0, 100, 300, or 1000 mg/kg/day (assuming 100% purity). The test material was applied 6 to 6.5 hours/day, 5 days/week for 3 weeks to a clipped dorsal area of skin (approximately 10% of the body surface) and covered with a gauze patch moistened with 1 ml reverse osmosis water per gram of test material. Clinical observations, dermal irritation evaluations, and measurements of body weight and food consumption were made at regular intervals. Hematology and serum chemistry tests, and terminal gross necropsies were performed on treatment day 21. Skin and selected tissues were examined for histopathology. The only treatment-related effects reported were transient desquamation on day 11 in 3/5 males at 300 mg/kg/day and 3/5 males at 1000 mg/kg/day, and enlarged livers in males at 1000 mg/kg/day (NOEL = 100 mg/kg). **No adverse effect was indicated. The study was acceptable (S. Morris and J. Gee, 2/8/99).

155-033; 116322; ANinety-day Toxicity Study in Rats with Technical Naphthalene Acetic Acid, Final Report,@ CDC-AM-006-78; W. E. Field; CDC Research, Inc., Clarks Summit, PA; 3/10/79. Groups of 20 or 30 (control and high dose) Sprague-Dawley rats / sex were fed diets containing naphthalene acetic acid (no lot #, purity not stated) for 90 days that produced exposures of approximately 0, 50, 150, or 500 mg/kg/day (measured values were 95 to 100% of nominal values). Ten high-dose and 10 control rats/sex were sacrificed after 29/30 days and the remaining rats sacrificed at 90 days. There were no treatment- related effects on behavior, clinical signs, food consumption, urinalysis, gross necropsy, or histopathology. Treatment-related effects included decreased bodyweight gain, and increased serum alkaline phosphatase levels in both sexes at 500 mg/kg/day; decreased hematocrit, hemoglobin, red blood count in males and increased female liver

weights at 500 mg/kg/day (NOEL = 150 mg/kg/day). The study was unacceptable because the rats were 16 weeks old at start and there was no ophthalmology, limited clinical chemistry and hematology data. The study was unacceptable. No worksheet was done (S. Morris and J. Gee, 11/30/99).

**309-011; 143808; A90-Day Subchronic Oral Toxicity Study in the Rat with 1-Naphthaleneacetamide (1-NAD),@ Lab. Project ID 183470B; G. W. Trimmer; Exxon Biomedical Sciences, Inc., East Millstone, NJ; 11/15/95. Groups of 10 Crl:CD BR rats/sex were fed diets containing 1-naphthaleneacetamide (lot # I940415, 99%) at 0, 250, 1000, or 4000 ppm for 90 days. There were no mortalities and no treatment-related clinical signs, ophthalmoscopic findings, or changes in hematology, serum chemistry, urine chemistry. Treatment-related effects included decreased body weight gains (group mean body weights were always greater than 85% [M] and 89% [F] of controls), decreased food consumption (M: 11-12%, F: 2-20%), increased mean relative liver weights, and hypertrophied centrilobular hepatocytes in both sexes (M: 5/10, F: 8/10 versus 0/10 for male and female controls) at 4000 ppm (NOEL = 1000 ppm). The study was acceptable. No worksheet was done (S. Morris and J. Gee, 11/30/99).

**309-012; 143810; A90-Day Subchronic Oral Toxicity Study in the Rat with 1-Naphthaleneacetic Acid Ethyl Ester (1-NAAEt),@ Lab. Project ID 183570; G. W. Trimmer; Exxon Biomedical Sciences, Inc., East Millstone, NJ; 11/15/95. Groups of 10 Crl:CD BR rats/sex were fed diets containing 1-naphthaleneacetic acid ethyl ester (lot # AM315002, 97.7%) at 0, 400, 2000, or 8000 ppm for 90 days. There were no mortalities and no treatment-related clinical signs, ophthalmoscopic findings, or changes in hematology, serum chemistry, urine chemistry. Treatment-related effects included decreased group mean body weight gains (group mean body weights were always greater than 87% [M] and 79% [F] of controls) and food consumption in both sexes at 8000 ppm and increased mean relative liver weights in both sexes at 8000 ppm (NOEL = 2000 ppm). No treatment-related histopathology findings were reported. The study was acceptable. No worksheet was done (S. Morris and J. Gee, 11/30/99).

309-014; 143813: AA 13-Week Oral (Capsule) Toxicity Study of 1-Naphthaleneacetic Acid, Ethyl Ester (1-NAAET) in the Beagle Dog,@ Lab. Project ID 86452; D. Farrell; Bio-Research Laboratories Ltd., Senneville, Quebec, Canada; 10/4/95. Groups of 4 beagle dogs/sex were given oral doses of 1-naphthaleneacetic acid, ethyl ester (lot # AM315002, 97.75%, gelatin capsules) for 13 weeks at 0, 40, 125, or 400 mg/kg/day. There were no mortalities and no treatment-related changes seen in food consumption, ophthalmology, hematology, clinical chemistry, urinalysis, organ weights, or gross or histopathology. Treatment-related effects included soft or liquid feces and decreased body weight gain in both sexes at 400 mg/kg/day (NOEL = 125 mg/kg/day). The complete study was not evaluated for acceptability. No worksheet was done (S. Morris, 3/18/99).

**309-013; 143812: AA 13-Week Oral (Capsule) Toxicity Study of 1-Naphthaleneacetamide (1-NAD) in the Beagle Dog,@ Lab. Project ID 86451; D. Farrell; Bio-Research Laboratories Ltd., Senneville, Quebec, Canada; 10/20/95. Groups of 4 beagle dogs/sex were given oral doses of 1-naphthaleneaceamide (lot # I940415, 98.7%, gelatin capsules) for 13 weeks at 0, 30, 100, or 300 mg/kg/day. There were no mortalities and no treatment-related changes seen in food consumption, ophthalmology, clinical chemistry, urinalysis, organ weights, or gross pathology. Treatment-related effects seen at 300 mg/kg/day included soft, liquid, or black feces in both sexes; slight decrease in body weight gain in males (grouped mean body weight always >94% of control); and evidence of hemolytic effects - decreased red blood cell counts, hemoglobin, and hematocrit; increased platelet values, bilirubin (females different from controls [P< 0.05] by registrant=s statistics), liver and spleen pigment, and bone marrow hematopoiesis (6/8) in both sexes, and increased blood cell volumes in males (NOEL = 100 mg/kg/day). The study was acceptable. No worksheet was done (S. Morris and J. Gee, 11/30/99).

309-016; 145805; AThe Metabolism of [^{14}C]-Naphthaleneacetamide in the Rat Following Oral

Administration,@ IRI Project No. 154791; G. Y. McCorquodale and M. S. Prout: Inveresk Research International, Tranent, Scotland; 3/29/96. Groups of 5 Sprague Dawley rats/sex were given [^{14}C]-1-naphthaleneacetamide (corn oil vehicle) by oral gavage. Group B received 1 mg/kg of labeled material. Group C received unlabeled compound at 1 mg/kg/day for 14 days immediately followed an day 15 by 1 mg/kg of labeled material. Group D received 100 mg/kg of labeled compound. Total urine and feces were collected over specified intervals for 168 hours post dosing. At 168 hours all animals were sacrificed and tissues and body fluids retained. Total radioactivity was measured in urine, feces, cage wash, tissues, and organs. Urine and fecal samples were pooled by sex and group. ^{14}C -labeled compounds in urine and feces were extracted with solvents and analyzed by HPLC. Recovery of ^{14}C in all groups approached 100%. Urine accounted for about 70% of the excreted ^{14}C and feces approximately 20 - 30%. Excretion was essentially complete at 24 hours. Tissues and body fluids contained 0.11 to 0.33% of the total ^{14}C. The highest concentrations were in whole blood, liver, and kidney. Major urinary metabolites were glycine (groups B, C, and D) and glucuronide (group D) conjugates. The major fecal metabolite was a polar compound, possibly a dihydrodiol. Other metabolites included naphthalene acetic acid, hydroxy-naphthalene acetic acid, and parent compound. The study was unacceptable because the intravenous route was not used and there was no rationale for the high dose (S. Morris and J. Gee, 11/30/99).

These records were evaluated.

00155-021	037200
00155-021	037201
00155-021	037202
00155-021	037203
00155-021	037204
00155-021	037205
00155-021	037199
00155-022	037207
00155-022	037207
00155-022	037296
00155-033	116322
00155-034	116326
00155-035	116327
00155-036	116328
00155-036	116328
00155-036	116330
00155-036	116334
00155-037	116335
00155-037	116339
00155-037	116341
00155-037	116343
00155-037	116346
00155-037	116347
00155-037	116348
00155-037	116349
00155-037	no record
00155-043	139924
00155-043	139925
00155-044	139926
00155-044	139927
00155-045	139928
00155-045	139929
00309-011	143808
00309-012	143810
00309-013	143812
00309-014	143813
00309-016	145805
50784-003	126288
50784-004	126739
50784-005	128553
50784-006	128691
50784-007	138882
50784-008	141498
50784-008	141498
50784-008	141498
50784-008	141498
50784-010	150752